WHAT IS CLAIMED IS:

1. A method of repairing a mutated exon of a pre-mRNA in a mammalian cell, comprising the steps of incorporating a DNA in the mammalian cell, which DNA encodes a repair RNA in the form of a pre-mRNA comprising a non-mutated exon with at least one flanking outron, and replacing the mutated exon of a damaged cellular RNA by the non-mutated exon of the repair RNA via RNA trans-splicing by means of splicing components naturally occurring in the cell, thereby repairing the mutated exon.

2. The method according to claim 1,
characterized in that
the incorporated DNA has a nucleotide sequence comprising a replication origin, an RNA polymerase-II promoter and a signal sequence at the 3' end for pre-mRNA polyadenylation.

3. The method according to claim 1,
characterized in that
a 5' outron and/or a 3' outron with at least ten nucleotides is employed in the repair RNA derived from said DNA.

4. The method according to any of claim 1,
characterized in that
each outron in the repair RNA has at least one antisense sequence which undergoes antisense pairing over a length of at least 18 bases to the mutated exon and/or to a flanking intron region of the mutated exon.

5. The method according to claim 1,
characterized in that
in said repair RNA the antisense sequence in the 5' outron pairs to the intronic polypyrimidine base sequence of a 3' splice site of the mutated exon, and this

antisense sequence in the 3' outron pairs to the intronic nucleotide sequence of a 5' splice site of the mutated exon.

6. The method according to claim 1,
characterized in that
in said repair RNA the 5' outron has a branch A site, a polypyrimidine base stretch and an AG dinucleotide at the border to the repair exon as components of the 3' splice site, and the 3' outron has a GU dinucleotide at the border to the repair exon as essential component of the 5' splice site.

7. The method according to claim 1,
characterized in that
in said repair RNA in the 5' outron the branch A site of the 3' splice site has the 8-mer sequence U-A/G-C/U-U-A/G-A-C/U-A/G and the polypyrimidine base stretch has the sequence of 15 to 18-mer (U/C), and in the 3' outron the intronic portion of the 5' splice site has the 6-mer sequence G-U-A/G-A/G-G-U.

8. The method according to claim 1,
characterized in that
in said repair RNA the repair exon, in addition to the non-mutated wild type sequence, has the 3-mer sequence A/G-A/G-G as exonic 5' splice site at the 3' end thereof, provided the repair exon is followed by an outron and, compared to the homologous wild type exon sequence, no other 1 or 2 amino acids are coded for by this sequence.

9. The method according to claim 1,
characterized in that
in said repair RNA the repair exon, in addition to the non-mutated wild type sequence, comprises at least one exonic splice enhancer (ESE) sequence as a result of modifying some nucleotides, no additional or other amino acids compared to the wild type exon sequence being coded for by said ESE sequence(s).

10. The method according to claim 1,
characterized in that
in said repair RNA the repair exon, as an alternative to the non-mutated wild type sequence of this exon only, also has a cDNA sequence, which is derived from several exons including the exon to be repaired, with the non-mutated sequence.

11. The method according to claim 1,
characterized in that
the repair RNA comprises only one single, distal 3' outron, provided the DNA of the repair exon has a cDNA sequence starting from exon 1 of the RNA to be repaired and ending with the exon to be repaired.

12. The method according to claim 1,
characterized in that
the repair RNA comprises only one single, proximate 5' outron, provided the DNA of the repair exon has a cDNA sequence starting with the exon to be repaired and ending with the last exon including the polyadenylation site of the RNA to be repaired.

13. A trans-splicing RNA-encoding DNA
characterized in that
said DNA has a nucleotide sequence comprising a replication origin, an RNA polymerase-II promoter and a signal sequence at the 3' end for pre-mRNA polyadenylation.

14. The repair RNA-encoding DNA according to claim 13,
characterized in that
a 5' outron and/or a 3' outron with at least ten nucleotides is included in the repair RNA derived from said DNA.

15. The repair RNA-encoding DNA according to claim 13,
characterized in that
each outron in the repair RNA has at least one antisense sequence which undergoes antisense pairing over a length of at least 18 bases to the mutated exon and/or to a flanking intron region of the mutated exon.

16. The repair RNA-encoding DNA according to claim 13,
characterized in that
in said repair RNA the antisense sequence in the 5' outron pairs to the intronic polypyrimidine base sequence of a 3' splice site of the mutated exon, and this antisense sequence in the 3' outron pairs to the intronic nucleotide sequence of a 5' splice site of the mutated exon.

17. The repair RNA-encoding DNA according to claim 13,
characterized in that
in said repair RNA the 5' outron has a branch A site, a polypyrimidine base stretch and an AG dinucleotide at the border to the repair exon as components of the 3' splice site, and the 3' outron has a GU dinucleotide at the border to the repair exon as essential component of the 5' splice site.

18. The repair RNA-encoding DNA according to claim 13,
characterized in that
in said repair RNA in the 5' outron the branch A site of the 3' splice site has the 8-mer sequence U-A/G-C/U-U-A/G-A-C/U-A/G and the polypyrimidine base stretch has the sequence of 15 to 18-mer (U/C), and in the 3' outron the intronic portion of the 5' splice site has the 6-mer sequence G-U-A/G-A/G-G-U.

19. The repair RNA-encoding DNA according to claim 13,
characterized in that
in said repair RNA the repair exon, in addition to the non-mutated wild type sequence, has the 3-mer sequence A/G-A/G-G as exonic 5' splice site at the 3' end

thereof, provided the repair exon is followed by an outron and, compared to the homologous wild type exon sequence, no other 1 or 2 amino acids are coded for by this sequence.

20. The repair RNA-encoding DNA according to claim 13,
characterized in that
in said repair RNA the repair exon, in addition to the non-mutated wild type sequence, comprises at least one exonic splice enhancer (ESE) sequence as a result of modifying some nucleotides, no additional or other amino acids compared to the wild type exon sequence being coded for by said ESE sequence(s).

21. The repair RNA-encoding DNA according to claim 13,
characterized in that
in said repair RNA the pertaining DNA of the repair exon, as an alternative to the non-mutated wild type sequence of this exon only, also has a cDNA sequence, which is derived from several exons including the exon to be repaired, with the non-mutated sequence.

22. The repair RNA-encoding DNA according to claim 13,
characterized in that
the repair RNA comprises only one single, distal 3' outron, provided the DNA for the repair exon has a cDNA sequence starting from exon 1 of the RNA to be repaired and ending with the exon to be repaired.

23. The repair RNA-encoding DNA according to claim 13,
characterized in that
the repair RNA comprises only one single, proximate 5' outron, provided the DNA for the repair exon has a cDNA sequence starting with the exon to be repaired and ending with the last exon including the polyadenylation site of the RNA to be repaired.

24. A method for the selective destruction of tumor cells in a cell population, comprising the steps of introducing a DNA into the cell population, which DNA encodes an artificially shortened cell death pre-mRNA, said cell death pre-mRNA being extended selectively at the N terminus via trans-splicing by means of RNA components occurring in the tumor cells, which include an AUG codon as start of translation, and naturally occurring splicing components, thus obtaining a complete cell death pre-mRNA and encoding a complete cell death protein selectively destroying the tumor cells on a direct or indirect route.

25. The method according to claim 24,
characterized in that
said DNA has a nucleotide sequence comprising a replication origin, an RNA polymerase-II promoter and a signal sequence at the 3' end for pre-mRNA polyadenylation.

26. The method according to claim 24,
characterized in that
the shortened cell death pre-mRNA derived from said DNA comprises an anterior 5' outron and an exon, the DNA of the exon in the distal portion thereof having a nucleotide sequence as cDNA which encodes from amino acid 2 on and up to the last amino acid of the cell death protein.

27. The method according to claim 24,
characterized in that
in the shortened cell death pre-mRNA the 5' end of the exon has a frame shift sequence of 0, 1 or 2 nucleotides.

28. The method according to claim 24,
characterized in that
in the shortened cell death pre-mRNA the exon downstream of the frame shift nucleotide sequence and upstream of the nucleotide sequence from amino acid 2

of the cell death protein on comprises a nucleotide sequence of a protease recognition region encoding a peptide sequence which can be cleaved by naturally occurring, cellular proteases.

29. The method according to claim 24,
characterized in that
in the shortened cell death pre-mRNA the exon has an exonic splice enhancer (ESE) sequence in the region of the protease recognition region and/or in the region of the cell death protein region encoding from amino acid 2 on, with no additional or other amino acids being coded for by said ESE sequence(s).

30. The method according to claim 24,
characterized in that
in the shortened cell death pre-mRNA the outron in the distal region towards the exon has a 3' splice site comprising a branch A site, a polypyrimidine base stretch and an AG dinucleotide at the border to the exon.

31. The method according to claim 24,
characterized in that
in the shortened cell death pre-mRNA the branch A site of the 3' splice site has the 8-mer sequence U-A/G-C/U-U-A/G-A-C/U-A/G and the polypyrimidine base stretch has the sequence of 15 to 18-mer (U/C).

32. The method according to claim 24,
characterized in that
the shortened cell death pre-mRNA in the outron upstream of the 3' splice site thereof comprises an antisense sequence of at least 18 nucleotides which undergo specific antisense pairing to a particular tumor pre-mRNA.

33. The method according to claim 24,

characterized in that

the antisense sequence in the 5' outron of the incomplete cell death pre-mRNA pairs to the specific tumor cell pre-mRNA in its polypyrimidine base sequence of the 3' splice site upstream of the second coding exon of said RNA.

34. The method according to claim 24,

characterized in that

in the shortened cell death pre-mRNA the 5' outron has a translation start AUG which is not in the reading frame of the exon for the cell death protein from amino acid 2 on, and which initiates a short nonsense protein.

35. A modified cell death RNA-encoding DNA comprising an RNA-encoding DNA according to claim 13,

characterized in that

a shortened cell death pre-mRNA comprises an anterior 5' outron and an exon, the DNA of the exon in the distal portion thereof having a nucleotide sequence as cDNA which encodes from amino acid 2 on and up to the last amino acid of the cell death protein.

36. The modified cell death RNA-encoding DNA according to claim 35,

characterized in that

in the shortened cell death pre-mRNA the 5' end of the exon has a frame shift sequence of 0, 1 or 2 nucleotides.

37. The modified cell death RNA-encoding DNA according to claim 35,

characterized in that

in the shortened cell death pre-mRNA the exon downstream of the frame shift nucleotide sequence and upstream of the nucleotide sequence from amino acid 2 of the cell death protein on comprises a nucleotide sequence of a protease recognition

region encoding a peptide sequence which can be cleaved by naturally occurring, cellular proteases.

38. The modified cell death RNA-encoding DNA according to claim 35, characterized in that

in the shortened cell death pre-mRNA the exon has an exonic splice enhancer (ESE) sequence in the region of the protease recognition region and/or in the region of the cell death protein region encoding from amino acid 2 on, with no additional or other amino acids being coded for by said ESE sequence(s).

39. The modified cell death RNA-encoding DNA according to claim 35, characterized in that

in the shortened cell death pre-mRNA the outron in the distal region towards the exon has a 3' splice site comprising a branch A site, a polypyrimidine base stretch and an AG dinucleotide at the border to the exon.

40. The modified cell death RNA-encoding DNA according to claim 35, characterized in that

in the shortened cell death pre-mRNA the branch A site of the 3' splice site has the 8-mer sequence U-A/G-C/U-U-A/G-A-C/U-A/G, and the polypyrimidine base stretch has the sequence of 15 to 18-mer (U/C).

41. The modified cell death RNA-encoding DNA according to claim 35, characterized in that

the shortened cell death pre-mRNA in the outron upstream of the 3' splice site thereof comprises an antisense sequence of at least 18 nucleotides which undergo specific antisense pairing to a particular tumor pre-mRNA.

42. The modified cell death RNA-encoding DNA according to claims 35, characterized in that

in the shortened cell death pre-mRNA the antisense sequence in the 5' outron of the incomplete cell death pre-mRNA pairs to the specific tumor cell pre-mRNA in its polypyrimidine base sequence of the 3' splice site upstream of the second coding exon of said RNA.

43. The modified cell death RNA-encoding DNA according to claim 35, characterized in that

in the shortened cell death pre-mRNA the outron has a translation start AUG which is not in the reading frame of the exon for the cell death protein from amino acid 2 on, and which initiates a short nonsense protein.

44. A method for the identification of potential trans-splice sites in cellular pre-mRNAs and for the subsequent identification of natural cellular trans-spliced RNAs, comprising the steps of introducing a DNA is introduced into cells, which DNA encodes an RNA probe which merely has either one 5' or one 3' splice site, said RNA probe interacting in the splice site thereof with a potent trans-splice site of a cellular pre-mRNA to form a trans-spliced RNA, the trans-spliced RNA being amplified in a cDNA PCR and sequenced in the portion from the unknown cellular RNA, an additional PCR analysis being performed thereafter, wherein the two primers being used undergo pairing to two particular, previously sequenced exonic portions from the two trans-spliced cellular RNAs, to determine whether the two particular trans-spliceable cellular RNAs would form trans-spliced hybrid RNAs *in vivo* which can be detected via said cDNA PCR.

45. The method according to claim 44,

characterized in that

said DNA encoding the probe RNA has a nucleotide sequence comprising a replication origin, an RNA polymerase-II promoter and a signal sequence at the 3' end for pre-mRNA polyadenylation.

46. The method according to claim 44,

characterized in that

the probe RNA is a pre-mRNA with 150-250 nucleotides in the case of no protein-encoding sequences in the exon region, or with some hundred nucleotides in the case of protein-encoding sequences in the exon region, which RNA has one single 5' or 3' splice site and therefore one exon and one outron.

47. The method according to claim 44,

characterized in that

the outron in a portion of the probe RNA molecules has a sequence of 12 to 18 uracil nucleotides and, in addition, invariably has a 8 to 12-mer recognition and cleavage nucleotide sequence for a restriction enzyme.

48. The method according to claim 44,

characterized in that

the probe RNA with a 3' splice site in the proximate 5' outron has a branch A site, a polypyrimidine base stretch and an AG dinucleotide at the border to the exon as components of a 3' splice site.

49. The method according to claim 44,

characterized in that

in the probe RNA with a 3' splice site the branch A site has the 8-mer sequence U-A/G-C/U-U-A/G-A-C/U-A/G and the polypyrimidine base stretch has the sequence of 15 to 18-mer (U/C).

50. The method according to claim 44,

characterized in that

in a probe RNA with a 3' splice site the DNA of the exon has the incomplete cDNA sequence of a small, easily detectable protein from amino acid 2 on, which merely lacks the ATG start of translation.

51. The method according to claim 44,

characterized in that

in a probe RNA with a 5' splice site this RNA has the 3-mer sequence A/G-A/G-G at the end of the exon, followed by the 6-mer sequence G-U-A/G-A/G-G-U at the beginning of the following distal 3' outron.

52. The method according to claim 44,

characterized in that

the RNA trans-splicing products consisting of the exonic portion of the probe RNA and the exonic portion of an initially unknown cellular RNA are first converted into an ss-cDNA and then into a ds-cDNA which, following addition of a restriction enzyme cleaving a specific restriction enzyme recognition nucleotide sequence in the outron portion thereof, is specifically amplified by means of a PCR and subsequently sequenced.

53. The method according to claim 44,

characterized in that

in the analysis of RNA trans-splicing products using a probe RNA with a 5' splice site, the ss-cDNA synthesis is effected with a reverse transcriptase and with a 55-mer primer of sequence N40-T15, and the subsequent ds-cDNA synthesis is effected with a DNA polymerase and an 18 to 24-mer primer homologous to a corresponding sequence in the exon of the probe RNA.

54. The method according to claim 44,

comprising the further steps of

analyzing the RNA trans-splicing products using a probe RNA with a 5' splice site, the subsequent first PCR amplification of the ds-cDNA being performed with

(a) an 18 to 24-mer primer equivalent to the anterior 5'-N-nucleotide sequence of primer N40-T15, and

(b) an 18 to 24-mer primer which is identical with the primer for ds-cDNA synthesis and binds to the exon of the probe RNA,

and the subsequent (nested) second PCR amplification being performed with

(c) an 18 to 24-mer primer equivalent to the far N-nucleotide sequence of primer N40-T15, and

(d) an 18 to 24-mer primer which also binds to the RNA probe exon, but does so downstream of primer (b) of the first PCR.

55. The method according to claim 44,

characterized in that

in the analysis of RNA trans-splicing products using a probe RNA with a 3' splice site, the ss-cDNA synthesis is effected with a reverse transcriptase and with a 15-mer primer and, 15-60 minutes after starting the ss-cDNA synthesis and after lowering the reaction temperature to about 30°C, with an additional, 48-mer primer of sequence N40-G8, and the subsequent ds-cDNA synthesis is effected with a DNA polymerase and an 18 to 24-mer primer equivalent to the anterior 5'-N-nucleotide sequence of primer N40-G8.

56. The method according to claim 44,

characterized in that

in the analysis of RNA trans-splicing products using a probe RNA with a 3' splice site, the subsequent first PCR amplification of the ds-cDNA is performed with

(a) an 18 to 24-mer primer equivalent to the anterior 5'-N-nucleotide sequence of primer N40-G8 according to claim 56, and

(b) an 18 to 24-mer primer binding to the ds-DNA probe exon of the probe RNA,

and the subsequent second PCR amplification is performed with

(c) an 18 to 24-mer primer equivalent to the far N-nucleotide sequence of primer N40-G8, and

(d) an 18 to 24-mer primer which also binds to the probe exon, but does so downstream of primer (b) of the above, first PCR.

57. The method according to claim 44,

characterized in that

the subsequent sequence analysis of the PCR products obtained is performed with one of the two primers (a) or (b), or, in the case of a nested PCR, with one of the two primers (c) or (d) of claim 54 or 56.

58. A probe RNA-encoding DNA for th e RNA-encoding DNA according to claim 13,

characterized in that

the probe RNA is a pre-mRNA with 150-250 nucleotides in the case of no protein-encoding sequences in the exon region, or with some hundred nucleotides in the case of protein-encoding sequences in the exon region, which RNA has one single 5' or 3' splice site and therefore one exon and one outron.

59. The probe RNA-encoding DNA according to claim 58,

characterized in that

in the probe RNA the outron in a portion of the RNA molecules has a sequence of 12 to 18 uracil nucleotides and, in addition, invariably has an 8 to 12-mer recognition and cleavage nucleotide sequence for a restriction enzyme.

60. The probe RNA-encoding DNA according to claim 58,

characterized in that

the probe RNA with a 3' splice site in the proximate 5' outron has a branch A site, a polypyrimidine base stretch and an AG dinucleotide at the border to the exon as components of a 3' splice site.

61. The probe RNA-encoding DNA according to claim 58,

characterized in that

in the probe RNA with a 3' splice site the branch A site has the 8-mer sequence U-A/G-C/U-U-A/G-A-C/U-A/G, and the polypyrimidine base stretch has the sequence of 15 to 18-mer (U/C).

62. The probe RNA-encoding DNA according to claim 58,
characterized in that
in a probe RNA with a 3' splice site said RNA-encoding DNA in the exon thereof has the incomplete cDNA sequence of a small, easily detectable protein from amino acid 2 on, which merely lacks the ATG start of translation.

63. The probe RNA-encoding DNA according to claim 58,
characterized in that
in a probe RNA with a 5' splice site this RNA has the 3-mer sequence A/G-A/G-G at the end of the exon, followed by the 6-mer sequence G-U-A/G-A/G-G-U at the beginning of the following distal 3' outron.

64. A method for the subsequent identification of natural cellular trans-spliced RNAs, comprising the steps of performing a cDNA PCR analysis to determine whether two particular trans-spliceable cellular RNAs will form trans-spliced hybrid RNAs *in vivo* which can be detected via said PCR analysis, wherein the two primers being used undergo pairing to two previously sequenced exonic portions from the cellular RNAs trans-spliced to two RNA probes.

65. A kit for the identification of trans-splice sites in a cellular pre-mRNA, comprising
two DNAs to encode a probe RNA with a 5' splice site or a probe RNA with a 3' splice site according to claim 45, also comprising a restriction enzyme cutting a specific sequence in the ds-cDNA of the probe RNA in the outron thereof, as well as primers for specific cDNA synthesis, PCR amplification and sequence analysis of the RNA trans-splicing products of cellular RNA portions and exon portions of the probe RNAs, and further comprising methodical instructions for the identification of trans-splice sites in cellular RNAs and the subsequent detection of natural, cellularly trans-spliced hybrid RNAs.